DOCKET NO.: ISIS0003-101 (ISIS-5030) PATENT

Amendments To The Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Please delete claims 96-132 as follows:

1. (previously presented) A method for eliciting modification of a selected RNA target in a cell comprising:

(a) providing a single-stranded RNA-like polynucleotide hybridizable with said RNA target;

(b) hybridizing the RNA-like polynucleotide and the RNA to form a polynucleotide-target duplex; and

(c) contacting the duplex with a polypeptide comprising an RNase III domain, under conditions selected to effect modification of the duplex by the polypeptide, and modification of the RNA target thereby.

2. (original) The method of claim 1 wherein said modification of the RNA target occurs in the cell's nucleus.

3. (original) The method of claim 1 wherein the polypeptide comprising an RNase III domain is an RNase III polypeptide.

4. (original) The method of claim 1 wherein the RNase III polypeptide is a human RNase III polypeptide.

5. (original) The method of claim 1 wherein modification of the selected RNA target is cleavage of the RNA target.

6. (original) The method of claim 1 wherein the polypeptide comprising an RNase III domain is present in enriched amounts.

7. (original) The method of claim 6 wherein the polypeptide comprising an RNase III domain present in enriched amounts is overexpressed or exogenously added.

8. (original) The method of claim 1 wherein the polypeptide comprising an RNase III domain is a purified RNase III polypeptide.

9. (original) The method of claim 1 wherein the RNA-like polynucleotide has a modification at the 2' position of at least one sugar.

10. (original) The method of claim 1 wherein step (c) is performed within a cell.

11. (original) The method of claim 1 wherein step (b) is performed within a cell.

12. (original) The method of claim 1 wherein step (b) is performed outside a cell.

13. (original) The method of claim 1 wherein at least one furanosyl moiety of the RNA-like polynucleotide is a ribofuranosyl moiety.

14. (original) The method of claim 13 wherein a majority of the furanosyl moieties of the RNA-like polynucleotide are ribofuranosyl moieties.

15. (original) A method for promoting gene silencing in a cell comprising providing to the cell, in an amount effective to promote said gene silencing, a polypeptide comprising an RNase III domain.

16. (original) The method of claim 15 wherein said promotion of gene silencing occurs in the cell's nucleus.

17. (original) The method of claim 15 wherein the polypeptide comprising an RNase III domain is an RNase III polypeptide.

18. (original) The method of claim 15 wherein the RNase III polypeptide is a human RNase III polypeptide.

19. (original) The method of claim 15 wherein the RNase III polypeptide is exogenously added.

20. (original) The method of claim 15 wherein the RNase III polypeptide is provided through upregulation of endogenous production of the polypeptide.

21. (original) The method of claim 15 wherein said RNase III polypeptide is a purified RNase III polypeptide.

22. (original) The method of claim 15 wherein said RNase III polypeptide is expressed by an exogenously added vector encoding said RNase III polypeptide.

23. (original) The method of claim 15 wherein said cell is a mammalian cell.

24. (original) The method of claim 15 wherein said cell is a human cell.

25. (original) A method for promoting gene silencing in a cell comprising enriching the amount or activity of RNase III polypeptide in said cell to a level effective to promote said gene silencing.

26. (original) The method of claim 25 wherein said promotion of gene silencing occurs in the cell's nucleus.

27. (original) The method of claim 25 wherein said enriching is by exogenous addition of RNase III polypeptide.

28. (original) The method of claim 27 wherein said exogenously added RNase III polypeptide is a purified RNase III polypeptide.

29. (original) The method of claim 25 wherein the RNase III polypeptide is provided through upregulation of endogenous production of the polypeptide.

30. (original) The method of claim 25 wherein said enriching is by addition of a vector encoding the RNase III polypeptide.

31. (original) The method of claim 25 wherein said cell is a mammalian cell.

32. (original) The method of claim 25 wherein said cell is a human cell.

33. (previously presented) A method for promoting gene silencing of a gene in a cell comprising:

(a) providing to said cell a single-stranded polynucleotide hybridizable with a target RNA encoded by a selected gene whose expression is to be silenced;

(b) hybridizing said polynucleotide and said target RNA to form a polynucleotide-target duplex; and

(c) contacting said duplex with a polypeptide comprising an RNase III domain, under conditions selected to effect cleavage or modification of the target RNA strand of the polynucleotide-target RNA duplex by the polypeptide comprising an RNase III domain, and silencing of the gene thereby.

34. (original) The method of claim 33 wherein said promotion of gene silencing occurs in the cell's nucleus.

35. (original) The method of claim 33 wherein the polypeptide comprising an RNase III domain is an RNase III polypeptide.

36. (original) The method of claim 33 wherein the RNase III polypeptide is a human RNase III polypeptide.

37. (original) The method of claim 36 wherein the human RNase III polypeptide comprises an amino acid sequence with at least 90% homology to SEQ ID NO: 2.

38-39. (cancelled).

40. (original) The method of claim 33 wherein the polynucleotide is an antisense oligonucleotide.

41. (original) The method of claim 33 wherein the polynucleotide is an RNA-like polynucleotide.

42. (original) The method of claim 33 wherein at least one sugar moiety of the polynucleotide is a ribofuranosyl sugar moiety.

43. (original) The method of claim 42 wherein at least 50% of the sugar moieties of the polynucleotide are ribofuranosyl sugar moieties.

44. (original) The method of claim 33 wherein the polynucleotide has at least one modification of the base, sugar or internucleoside linkage.

45. (original) The method of claim 44 wherein the polynucleotide has a modification at the 2' position of at least one sugar.

46. (original) The method of claim 33 wherein the RNase III polypeptide is present in enriched amounts.

47. (original) The method of claim 46 wherein the RNase III polypeptide present in enriched amounts is overexpressed or exogenously added.

48. (original) The method of claim 46 wherein the RNase III polypeptide is a purified RNase III polypeptide.

49. (original) The method of claim 46 wherein said enriching is by addition of a vector encoding said RNase III polypeptide.

50. (original) The method of claim 46 wherein the RNase III polypeptide is provided through upregulation of endogenous production of the polypeptide.

51. (original) The method of claim 33 wherein said cell is a mammalian cell.

52. (original) The method of claim 33 wherein said cell is a human cell.

53. (original) The method of claim 33 wherein said polynucleotide-target RNA duplex forms inside the cell.

54. (original) The method of claim 33 wherein said polynucleotide-target RNA duplex forms outside the cell.

55. (previously presented) A method for inhibiting the expression of a gene in a cell comprising providing to said cell an agent effective to elicit RNase III modification of double-stranded RNA in the cell, wherein the agent, when a polynucleotide, is single-stranded.

56. (original) The method of claim 55 wherein said inhibition of gene expression occurs in the cell's nucleus.

57. (original) The method of claim 55 wherein said agent is a nucleic acid which is hybridizable with an RNA encoded by the gene whose expression is to be inhibited.

58. (original) The method of claim 55 wherein said RNase III modification is RNase III cleavage.

59-60. (cancelled).

61. (previously presented) The method of claim 55 wherein the agent is an antisense oligonucleotide.

62. (previously presented) The method of claim 55 wherein the agent is an RNA-like polynucleotide.

63. (previously presented) The method of claim 55 wherein the agent is a polynucleotide and wherein at least one sugar moiety of the polynucleotide is a ribofuranosyl sugar moiety.

64. (original) The method of claim 63 wherein at least 50% of the sugar moieties of the polynucleotide are ribofuranosyl sugar moieties.

65. (previously presented) The method of claim 55 wherein the agent is a polynucleotide having at least one modification of the base, sugar or internucleoside linkage.

66. (original) The method of claim 65 wherein the polynucleotide has a modification at the 2' position of at least one sugar.

67. (previously presented) A method for promoting inhibition of expression of a gene in a cell comprising:

(a) providing to said cell a single-stranded polynucleotide hybridizable with a target RNA encoded by the gene whose expression is to be inhibited;

(b) hybridizing the polynucleotide and the target RNA to form a polynucleotide-target duplex; and

(c) contacting the duplex with a polypeptide comprising an RNase III domain, under conditions effective to effect cleavage or modification of the target RNA strand of the polynucleotide-target RNA duplex by the RNase III polypeptide, and inhibition of expression of the gene thereby.

68. (original) The method of claim 67 wherein said promotion of inhibition of gene expression occurs in the cell's nucleus.

69. (original) The method of claim 67 wherein the polypeptide comprising an RNase III domain is an RNase III polypeptide.

70. (original) The method of claim 69 wherein the RNase III polypeptide is a human RNase III polypeptide.

71. (original) The method of claim 70 wherein the human RNase III polypeptide comprises an amino acid sequence with at least 90% sequence identity to SEQ ID NO: 2.

72-73. (cancelled).

74. (original) The method of claim 67 wherein the polynucleotide is an antisense oligonucleotide.

75. (original) The method of claim 67 wherein the polynucleotide is an RNA-like polynucleotide.

76. (original) The method of claim 67 wherein at least one sugar moiety of the polynucleotide is a ribofuranosyl sugar moiety.

77. (original) The method of claim 76 wherein at least 50% of the sugar moieties of the polynucleotide are ribofuranosyl sugar moieties.

78. (original) The method of claim 67 wherein the polynucleotide has at least one modification of the base, sugar or internucleoside linkage.

79. (original) The method of claim 78 wherein the polynucleotide has a modification at the 2' position of at least one sugar.

80. (original) The method of claim 67 wherein the polypeptide comprising an RNase III domain is present in enriched amounts.

81. (original) The method of claim 80 wherein the polypeptide comprising an RNase III domain and present in enriched amounts is overexpressed or exogenously added.

82. (original) The method of claim 81 wherein the polypeptide comprising an RNase III domain and present in enriched amounts is a purified RNase III polypeptide.

83. (original) The method of claim 81 wherein said enriching is by addition of a vector encoding said polypeptide comprising an RNase III domain.

84. (original) The method of claim 67 wherein said cell is a human cell.

85. (original) The method of claim 67 wherein step (c) is performed within a cell.

86. (original) The method of claim 67 wherein step (b) is performed within a cell.

87. (original) The method of claim 67 wherein step (b) is performed outside a cell.

88. (original) A cell having enhanced RNase III activity over an activity exhibited by a second cell, said second cell not enriched with respect to the amount or activity of RNase III polypeptide.

89. (original) The cell of claim 88 wherein said enhanced RNase III activity is detectable in the cell's nucleus.

90. (original) The cell of claim 88 wherein said enhanced RNase III activity is due to overexpression of RNase III.

91. (original) The cell of claim 88 wherein the RNase III polypeptide is provided through upregulation of endogenous production of the RNase III polypeptide.

92. (original) The cell of claim 88 wherein said enhanced RNase III activity is due to exogenously added RNase III.

93. (previously presented) A method for eliciting modification of an RNA target in a cell comprising:

(a) providing a single-stranded RNA-like polynucleotide hybridizable with said RNA target;

(b) hybridizing the RNA-like polynucleotide and the RNA to form a polynucleotide-target duplex; and

(c) contacting the duplex with a polypeptide comprising an RNase III domain, under conditions selected to effect modification of the duplex by the polypeptide, and modification of the RNA target thereby.

94. (original) A hybrid RNase III comprising at least one domain from a human RNase III and at least one domain from an RNase III of an organism other than human.

95. (original) The hybrid RNase III of claim 94 wherein the non-human RNase III domain is derived from an organism selected from the group consisting of *E. coli*, *S. pombe*, *C. elegans* and *S. cerevisiae*.

96-132. (canceled).